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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,066	05/25/2001	Christopher W. Benjamin	0229US1/PHRM-0328	6862

34135 7590 06/03/2003

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/03/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/866,066	BENJAMIN ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-115* is/are pending in the application.

4a) Of the above claim(s) *1-29,35-73,76-88 and 95-115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35,74,75 and 89-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-115* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Information Disclosure Statements, submitted 19 July 2001 and 15 March 2002, have been entered into the record as Papers 7 and 10, respectively. Applicant's election with traverse of Invention II, (claims 30-35, 74, 75 and 89-94) in Paper No. 13 (20 March 2003) is acknowledged. In addition, Applicant elected the following invention: SEQ ID NO: 20. The Applicant traversed the restriction and argued that it would not constitute a serious burden to search several groups. However, Groups I-XIV were restricted properly because they comprise products which possess characteristic differences in structure and function. Furthermore, the methods of groups I, IV, VI, VII, IX, X, XII and XIV are independent and distinct in that they are practiced with materially different process steps for materially different purposes and each method requires a non-coextensive search because of different starting materials, process steps, and goals. Additionally, the sequences are independent and distinct products having characteristic differences in structure and function and having different uses. A complete search of the art for each sequence, as well as full database searches, constitute undue burden if all sequences are searches together.

Claims 1-29, 35-73, 76-88 and 95-115 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected Inventions, there being no allowable generic or linking claim.

Claims 30-35, 74, 75 and 89-94 are under examination in the current application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "ION157 ION CHANNEL POLYPEPTIDE".

Appropriate correction is requested.

URL's

The disclosure is objected to because it contains browser-executable code. This occurs, for example, on p. 79, last line. All URL's should be removed from the Specification. Applicant may refer to web sites by non-executable name only (e.g., "The BLAST program provided by NCBI"). See MPEP § 608.01 (p).

Appropriate correction is required.

Claim Rejections/Objections

Claim Objections

Claims 31-34,74, 75 and 90-93 are objected to for reciting non-elected subject matter (SEQ ID NO: 21-38, for example).

Appropriate correction is required.

Claims 30 and 89 are objected to for depending from non-elected claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

The following is a quotation of 35 U.S.C. 101:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode c ntemplated by the inventor of carrying ut his invention.

Claims 30-35, 74, 75 and 89-94 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to the polypeptide comprising SEQ ID NO: 20, homologous sequences, allelic variants, chimera and compositions comprising.

No well-established utility exists for newly isolated, complex biological molecules. However, the specification asserts the following as credible, specific and substantial patentable utilities for the claimed polypeptide and/or disclosed polynucleotide.

1) For the production of antibodies,

2) To make hybridization probes and primers to detect nucleic acid molecules that encode the polypeptide of SEQ ID NO: 20 and to localize gene expression in tissue samples,

3) To produce a variant or chimeric polypeptide,

4) In the creation of transgenic animals,

5) To detect pharmacogenomically-relevant polymorphisms in individuals,

6) To search for drugs as ligands or antagonists of the claimed polypeptide,

7) For gene therapy.

8) For use as an ion channel.

Each of these shall be addressed in turn:

1) For the production of antibodies. This asserted utility is credible, but not specific or substantial. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, both the polypeptide and its antibodies have no patentable utility.

2) To make hybridization probes and primers to detect nucleic acid molecules that encode the polypeptide of SEQ ID NO: 20 and to localize gene expression in tissue samples. This asserted utility is credible but not substantial or specific. Hybridization probes and primers can be designed from any polynucleotide sequence. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) To produce a variant or chimeric polypeptide. This asserted utility is credible but not substantial or specific. Such can be performed with any polypeptide or polynucleotide encoding a polypeptide. Further, the specification discloses nothing specific or substantial for the variant polypeptide that is produced by this method. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) In the creation of transgenic animals. This asserted utility is credible but not specific or substantial. The specification does not disclose a phenotype associated with a mutated, deleted, or translocated gene encoding the present invention. Significant further experimentation would be required of the skilled artisan to identify such a phenotype. The specification discloses nothing about whether the claimed gene will be "knocked in" or "knocked out" or what specific tissues and cells are being targeted. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

5) To detect pharmacogenomically-relevant polymorphisms in individuals. This asserted utility is credible, however it is neither specific nor substantial. Some examples of well-known polymorphisms occur in metabolic enzymes (e.g. the liver P450's or the dehydrogenases), and are very well characterized physiologically and within populations. Applicants have not

demonstrated the function of the claimed polypeptide of SEQ ID NO: 20, encoded by the disclosed polynucleotide of SEQ ID NO: 1, much less clinically-relevant polymorphisms. Thus, the asserted utility is not substantial. Finally, many unrelated sequences can be polymorphic, generally. Thus, the asserted utility is not specific.

6) To search for drugs as ligands or antagonists of the claimed polypeptide. This asserted utility is credible. However, it is not substantial or specific. The specification does not characterize the claimed polypeptide of SEQ ID NO: 20 or the disclosed polynucleotide of SEQ ID NO: 1. Therefore binding sites, etc. are not identified. Significant further experimentation would be required of the skilled artisan to characterize the protein and search for ligands. There is no disclosure for example, of how to assay for ligand binding and possible transduction mechanisms. It is not known the class of drugs to use or what measurements to perform. Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not substantial.

7) For gene therapy. This asserted utility is credible but not specific or substantial. Such can be performed for any polynucleotide. Thus the asserted utility is not specific. Further, the specification does not disclose diseases associated with a mutated, deleted, or translocated genes encoding the claimed invention. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease and to determine the route of administration of the gene, as well as quantity and duration of treatment. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

8) *For use as an ion channel.* This asserted utility is credible and specific, but not substantial. Members of this large family of proteins share several recognizable structural similarities, yet have diverse functions (see, for example: Suppl 1, Trends Pharmacol. Sci., 1997, 18: 77-84; Lehmann-Horn et al., 1999, Physiol Rev 79(4): 1317-1372). The specification does not disclose characteristics specific to a voltage-gated channel (e.g., Nernst potential, conductance, reversal potential, ion selectivity, etc), any blockers, its physiological role in the organism, or a link between the channel and a specific condition or disease state. Determination of any of these would require significant further research. Since the asserted utility is not available as a real world use, and significant further research beyond the disclosure is required, the asserted utility is not substantial.

Claims 30-35, 74, 75 and 89-94 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 30-35, 74, 75 and 89-94 are directed to a polypeptide comprising the amino acid sequence of SEQ ID NO: 20. The claims also recite a nucleic acid molecule that encodes the polypeptide of SEQ ID NO 20, compositions comprising and chimeric receptors. The specification teaches the polypeptide of SEQ ID NO: 20, the polynucleotide of SEQ ID NO: 1, and asserts the polypeptide is a new human ion channel. However, the specification does not teach functional or structural characteristics of the polypeptide or polynucleotide recited in the claims.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity.

Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologues must have different molecular and cellular functions. Furthermore, the specification asserts that the claimed polypeptide is an ion channel protein based on homology to known ion channels. This assertion cannot be accepted as credible in the absence of supporting evidence of specific function, because the art shows that structurally similar ion channels are unpredictably functionally dissimilar. For example, relevant literature reports that potassium channels constitute the most diverse class of ion channels with respect to kinetic properties, regulation, pharmacology, and structure (pg. 1329; Lehmann-Horn et al. Physiol Rev 79 (4): 1317-1372). Additionally, over 50 distinct channels have been identified in humans in both excitable and non-

excitable cell types. The channels are involved in the control of a variety of cellular functions, including neuronal firing, cellular proliferation, and neurotransmitter and hormone secretion.

Although ion channel family members share several common structural features, relevant art (pg 1329-1330; Lehmann-Horn et al. Physiol Rev 79(4): 1317-1372, 1999) shows that members of a class do not always share a specific and substantial functional attribute or utility, despite having structural features in common. Therefore, membership in a class of ion channels may not impart a specific, substantial, and credible utility to a new member, such as the claimed polynucleotide of the instant Application.

Based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotides to make a biologically active ion channel-like polypeptide without resorting to undue experimentation to determine what the specific biological activities of the polypeptide are.

The specification does not teach the skilled artisan how to use the claimed ion channel-like polypeptide for any purpose. Therefore, the skilled artisan is not provided with sufficient guidance to use the claimed polynucleotides for any purpose.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6)

the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Due to the large quantity of experimentation necessary to determine an activity or property of the claimed polypeptide such that it can be determined how to use the claimed polypeptide or disclosed polynucleotide encoding the ion channel-like polypeptide and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Furthermore, the specification does not reasonably provide enablement for use of an *allelic variant* as recited in claims 34 and 93. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Applicants have not identified allelic variants of the polynucleotide of SEQ ID NO: 1, nor localized it to a particular locus of a chromosome. Claims 34 and 93 encompass numerous undefined variants of SEQ ID NO: 1, without precise recitations of function that can be applied to allelic variants. Furthermore, as discussed above, it is not predictable as to which variants are tolerated while still maintaining the functional characteristics of a protein.

Furthermore, the specification does not reasonably provide enablement for use of a *chimeric receptor* as recited in claims 74 and 75. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Applicants have not produced or identified a chimeric receptor comprising SEQ ID NO: 20. Claims 74 and 75 encompass numerous undefined variants of SEQ ID NO: 20, without precise and enabled recitations of function that can be applied to a chimeric receptor. Furthermore, as discussed above, it is not predictable as to which variants are tolerated while still maintaining the functional characteristics of a protein.

35 U.S.C. 112, first paragraph- Written Description

Claims 34, 74, 75 and 93 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 34, 74, 75 and 93 are directed to allelic variants or chimera of an ion channel-like polypeptide (SEQ ID NO: 20) encoded by the polynucleotide of SEQ ID NO: 1.

The specification teaches a polynucleotide (SEQ ID NO: 1) and a polypeptide (SEQ ID NO: 20). However, the specification does not teach functional or structural characteristics of the claimed polypeptides or disclosed polynucleotides. The description of one polypeptide and one

. polynucleotide encoding *an ion channel polypeptide* (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide comprising SEQ ID NO: 20 encoded by the nucleotide sequence of SEQ ID NO: 1- which encodes a full-length polypeptide- but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, second paragraph-indefiniteness.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 33 and 92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32, 33 and 92 are rendered indefinite for reciting the phrase: "an amino acid sequence homologous to a sequence". It is not known the degree of homology required in the specified amino acid sequence (0%-100%); thus many unknown proteins are encompassed by the claims.

Similarly, claims 32, 33 and 92 are rendered indefinite for reciting the phrase: "at least one conservative amino acid substitution". "[A]t least one conservative amino acid substitution" could encompass an amino acid sequence in which all amino acids are substituted. Thus many unknown proteins are encompassed by the claims.

Conclusion: Claims 30-35, 74, 75 and 89-94 are rejected for the reasons listed above.

Claims 30-34, 74, 75 and 89-93 are objected to.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

SLW

5/20/03

ELIZABETH KEMMERER
PRIMARY EXAMINER